Preparation of New Nitrogen-Bridged Heterocycles. 69.[1] Synthesis and Reaction of 1-(α-Hydroxybenzyl)thieno-[3,4-b]indolizine Derivatives

Akikazu Kakehi,* Hiroyuki Suga, Yukihisa Okumura, Kennosuke Itoh, Shin Hatayama, Daisuke Kubo, and Kouji Kobayashi

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380–8553, Japan

ABSTRACT

The title compounds, 1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine derivatives, were obtained in good yields by the reduction of the corresponding 1-benzoylthieno[3,4-*b*]indolizines with sodium borohydride in refluxing ethanol. These compounds were considerably unstable and decomposed gradually even at room temperature, but, on exposure to acetic acid, unexpected condensation took place to afford α,α-bis(thieno[3,4-*b*]indolizin-1-yl)toluenes in low to moderate yields.

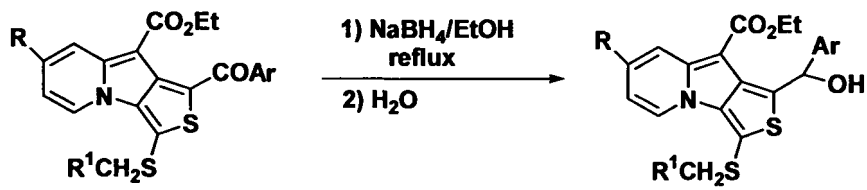
INTRODUCTION

Recently, we reported the intramolecular arene-arene and arene-π interactions of various ethyl 1-(arylcarbonyl)thieno[3,4-*b*]indolizine-9-carboxylate derivatives in which an aryl ring or an unsaturated linkage are connected with a sulfide spacer at the 3-position.[2-7] In the continuation of this work we next planned the introduction of an asymmetric center into these thieno[3,4-*b*]indolizine derivatives and the investigation of the conformational stability of the compounds obtained thus. As decribed in our preliminary communication,[8] the reduction of ethyl 1-arylcarbonyl-3-(benzylthio)thieno[3,4-*b*]indolizine-9-carboxylates as model compounds with sodium borohydride proceeded smoothly to afford the corresponding ethyl 3-benzylthio-1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine-9-carboxylates in good yields, but handling these compounds in the conformational studies was difficult because of their instability. However, further investigation of the decomposition reactions disclosed that the reduced products underwent a new type of self-condensation to be transformed into α,α-bis[3-(benzylthio)thieno[3,4-*b*]indolizin-1-yl]toluene derivatives and the extension of this reaction to other derivatives was also possible. In this paper we report the smooth preparation of the title compounds and their acid-catalyzed self-condensation reactions.

* Corresponding author. E-mail: *xkakehi@shinshu-u.ac.jp*

RESULTS AND DISCUSSION

Reduction of ethyl 1-benzoylthieno[3,4-*b*]indolizine-9-carboxylate derivatives. The selective reduction of the ketone carbonyl group in ethyl 1-benzoyl-3-(benzylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**1a**)[2] with sodium borohydride proceeded slowly in ethanol at room temperature, but at the reflux temperature, it smoothly reacted to provide ethyl 3-benzylthio-1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine-9-carboxylate (**2a**) in an excellent yield (99%). Similar treatment of other ethyl 1-(arylcarbonyl)thieno[3,4-*b*]indolizine-9-carboxylates (**1b—r**)[2] afforded the corresponding alcohols **2b—r** in 71—99% yields, respectively (Scheme 1).



1a—r **2a—r**

Prod.	React.	R	Ar	R^1	Yield (%)	Prod.	React.	R	Ar	R^1	Yield (%)
2a	**1a**	H	Ph	Ph	99	**2j**	**1j**	Me	Ph	Ph	85
2b	**1b**	H	*p*-ClC_6H_4	Ph	97	**2k**	**1k**	Me	*p*-ClC_6H_4	Ph	99
2c	**1c**	H	*p*-BrC_6H_4	Ph	72	**2l**	**1l**	Me	*p*-BrC_6H_4	Ph	86
2d	**1d**	H	Ph	H	97	**2m**	**1m**	Me	Ph	H	93
2e	**1e**	H	*p*-ClC_6H_4	H	83	**2n**	**1n**	Me	*p*-ClC_6H_4	H	93
2f	**1f**	H	*p*-BrC_6H_4	H	99	**2o**	**1o**	Me	*p*-BrC_6H_4	H	99
2g	**1g**	H	Ph	Me	98	**2p**	**1p**	Me	Ph	Me	71
2h	**1h**	H	*p*-ClC_6H_4	Me	92	**2q**	**1q**	Me	*p*-ClC_6H_4	Me	86
2i	**1i**	H	*p*-BrC_6H_4	Me	83	**2r**	**1r**	Me	*p*-BrC_6H_4	Me	93

Scheme 1

These products **2a—r** were obtained as yellow crystalline substances and their colors were clearly lighter than those of the original 1-arylcarbonyl derivatives **1a—r**, suggesting the fission of the conjugated system. Compounds **2a—r** were unstable and decomposed gradually even at room temperature in the crystalline state and smoothly in their chloroform solutions. This instability of **2a—r** may be caused by a further introduction of an electron-withdrawing group on the π-excess thiophene ring. The elemental analyses of products **2a—r** were in good accord with our proposed compositions and the IR spectra showed a considerably lowered ester carbonyl band (1620—1669 cm^{-1}) and a broad hydroxyl one (3281—3451 cm^{-1}).

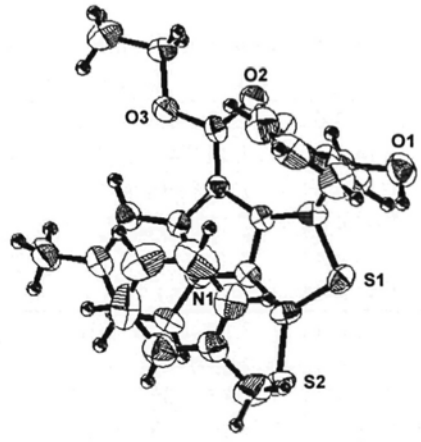


Figure 1. ORTEP drawing of **2j**

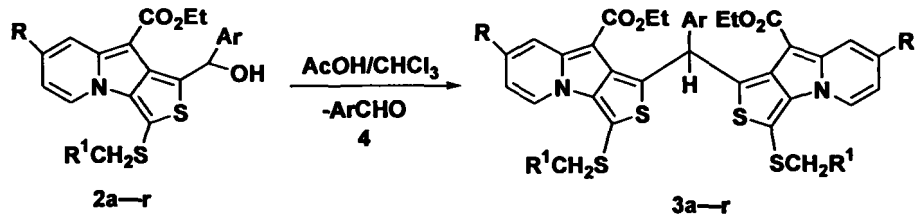
The ^{1}H-NMR spectra (Table 1) of **2a—r** exhibited a broad hydroxyl proton at δ 5.82—6.21 and a 1(1)-methine one at δ 6.45—6.57 as a singlet (**2b—d,j—m**) or a doublet (**2a,e—i,n—r**), together with other proton signals in these molecules. In addition, the chemical shifts for the 5- and 6-protons of 3-(benzylthio)thieno[3,4-*b*]indolizines (**2a—c,j—l**) were significantly shifted to higher magnetic regions (δ 0.24—0.44 ppm) in comparison with those of the 3-methylthio derivatives (**2d—f,m—o**), and these values of the chemical shifts were parallel with the relations (δ 0.1—0.3 ppm) between the ethyl 1-arylcarbonyl-3-(benzylthio)thieno[3,4-*b*]indolizine derivatives (**1a—c,j—l**) and the 3-methylthio derivatives (**1d—f,m—o**).[2] These facts supported that the structures of products **2a—c,j—l** must be the gauche conformations in the relation of the sulfide linkage in which an arene-arene interaction is possible. Fortunately, X-ray analysis for one compound (**2j**) was carried out and the conformation was in accord with our expected one. The ORTEP drawing[9] for the structure of **2j** is shown in Figure 1.

Table 1. ^{1}H-NMR Spectral data for 1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizines (**2a—r**)

No[a]	C-5	C-6	C-7	C-8	C-1(1)	OH	CO_2Et	Ar	R^1CH_2S
2a	8.72	6.37	7.16	8.03	6.54[b]	5.90	1.44 4.42	7.30—7.43[c] 7.56[d]	3.86 6.87—6.96[d] 7.02—7.11[c]
2b	8.74	6.39	7.17	8.03	6.48	5.93	1.44 4.41	7.34 7.47	3.88 6.92—6.96[d] 7.05—7.13[c]
2c	8.74	6.40	7.17	8.03	6.46	5.94	1.44 4.41	7.41 7.50	3.88 6.89—6.95[d] 7.00—7.14[c]
2d	9.16	6.65	7.27	8.13	6.57	5.81	1.45 4.44	7.31—7.42[c] 7.57[d]	2.39
2e	9.16	6.67	7.29	8.12	6.52[b]	5.92	1.45 4.43	7.35 7.50	2.41
2f	9.16	6.67	7.28	8.12	6.51[b]	5.92	1.45 4.43	7.44 7.51	2.41
2g	9.26	6.65	7.28	8.14	6.57[b]	5.92	1.45 4.44	7.32—7.44[c] 7.58[d]	1.22 2.76
2h	9.24	6.65	7.28	8.12	6.52[b]	5.97	1.45 4.42	7.35 7.50	1.23 2.77
2i	9.25	6.65	7.28	8.12	6.50[b]	5.96	1.45 4.43	7.44 7.50	1.23 2.77
2j	8.62	6.23	2.34	7.82	6.52	5.85	1.44 4.42	7.30—7.41[c] 7.55[d]	3.86 6.91—6.96[d] 7.03—7.12[c]
2k	8.64	6.25	2.35	7.81	6.47	5.98	1.44 4.41	7.34 7.47	3.87 6.92—6.96[d] 7.03—7.13[c]
2l	8.63	6.25	2.35	7.81	6.45	6.21	1.44 4.41	7.41 7.49	3.87 6.91—6.96[d] 7.03—7.13[c]
2m	9.03	6.49	2.40	7.91	6.55	5.82	1.44 4.44	7.31—7.42[c] 7.57[d]	2.37
2n	9.03	6.51	2.41	7.90	6.51[b]	5.91	1.45 4.43	7.35 7.50	2.39
2o	9.01	6.49	2.40	7.88	6.49[b]	5.90	1.44 4.42	7.44 7.50	2.39
2p	9.07	6.45	2.38	7.87	6.55[b]	5.88	1.44 4.42	7.28—7.44[c] 7.57[d]	1.29 2.72
2q	9.11	6.49	2.41	7.89	6.50[b]	5.95	1.45 4.42	7.34 7.50	1.22 2.75
2r	9.12	6.49	2.41	7.90	6.48[b]	5.95	1.45 4.42	7.44 7.50	1.22 2.77

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}$=6.8—7.1 Hz, $J_{7,8}$=9.3—9.5 Hz, $J_{5,7}$=0.8—1.0 Hz, $J_{6,8}$=1.1—1.3 Hz, J_{Et}=6.8—7.2 Hz, $J_{Ar(vicinal)}$=7.3—8.4 Hz. b) The coupling constant between the C1(1)-H and the hydroxy proton is 4.6—5.4 Hz. c) 3H. d) 2H.

Unexpected condensation reactions of 1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine derivatives. As described above, these reduction products **2a—r** were considerably unstable and often decomposed through their separation and purification processes. In particular, we observed the formation of compounds **3d** through the column chromatographic separation of **2d** on silica gel and that of **3j** in the trial of the recrystallization of **2j** from the chloroform solution, though these transformation reactions were less reproducible. As their structures by the ^{1}H-NMR spectral analyses of **3d,j** and the X-ray analysis for **3j** were decided to be α,α-bis(thieno[3,4-*b*]indolizin-1-yl)toluene derivatives[8] and thus the acid catalyzed condensation route from **2d,j** to **3d,j** could be presumed, we next attempted the generalization of this type of reaction. At first, alcohols **2a,d** were treated with weak acidic substances such as silica gel and phenols at room temperature or under heating conditions in various solvents, but they did not provide good results. On the other hand, the treatment of alcohols **2a,d** with strong acids such as trifluoroacetic acid, methanesulfonic acid and sulfuric acid caused only their decomposition. After many elaborations we found that this type of reaction proceeds in the presence of small amount of acetic acid in a chloroform solution of alcohol **2**. When alcohols **2a—r** were treated with 4 equivalent amounts of acetic acid in chloroform at room temperature for 1 day, the corresponding condensation products **3a—r** were obtained in variable yields (13—89%). (Scheme 2) In addition a singlet signal (δ 10.03 (benzaldehyde), 9.98 (*p*-chlorobenzaldehyde), or 9.97 ppm (*p*-bromobenzaldehyde)) due to an aromatic aldehyde proton could be detected in the ^{1}H-NMR spectra of these reaction mixtures, though their isolations



2a—r 3a—r

Prod.	React.	R	Ar	R^1	Yield (%)	Prod.	React.	R	Ar	R^1	Yield (%)
3a	2a	H	Ph	Ph	40	3j	2j	Me	Ph	Ph	25
3b	2b	H	*p*-ClC_6H_4	Ph	31	3k	2k	Me	*p*-ClC_6H_4	Ph	18
3c	2c	H	*p*-BrC_6H_4	Ph	22	3l	2l	Me	*p*-BrC_6H_4	Ph	13
3d	2d	H	Ph	H	51	3m	2m	Me	Ph	H	54
3e	2e	H	*p*-ClC_6H_4	H	81	3n	2n	Me	*p*-ClC_6H_4	H	89
3f	2f	H	*p*-BrC_6H_4	H	31	3o	2o	Me	*p*-BrC_6H_4	H	39
3g	2g	H	Ph	Me	41	3p	2p	Me	Ph	Me	38
3h	2h	H	*p*-ClC_6H_4	Me	51	3q	2q	Me	*p*-ClC_6H_4	Me	65
3i	2i	H	*p*-BrC_6H_4	Me	27	3r	2r	Me	*p*-BrC_6H_4	Me	76

Scheme 2

were unsuccessful because of the low concentration.

These products were obtained as black (**3a—c,j—l**) or yellow prisms (**3c—i,m—r**). They are considerably unstable and gradually decomposed when they were kept at room temperature. In addition, compounds (**3a—c,j—l**) having a 3-benzylthio group smoothly decomposed under the irradiation of any light. The elemental analyses of products **3a—r** were in good accord with our proposed compositions and the IR spectra showed a characteristic

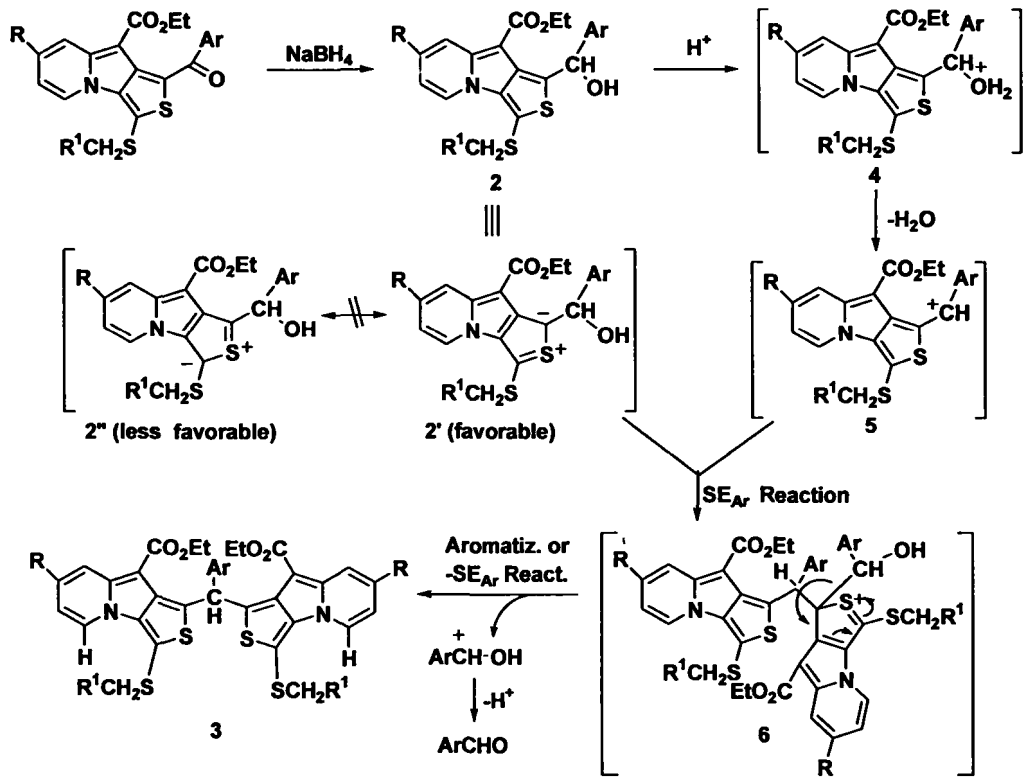
Table 2. ^{1}H-NMR Spectral data for a-aryl[α,α-bis(thieno[3,4-*b*]indolizin-1-yl)methanes (**3a-r**)

No[a]	C-5	C-6	C-7	C-8	C-1(1)	CO_2Et	Ar	R^1CH_2S
3a	8.75	6.35	7.09	8.17	7.73	1.05 4.03—4.22	6.97—7.16	3.87 6.92[b] 6.97—7.16
3b	8.76	6.37	7.11	8.16	7.75	1.09 4.14	c) 7.23	3.88 6.92[b] 6.98—7.10
3c	8.76	6.37	7.11	8.15	7.73	1.08 4.04—4.22	c) 7.38	3.87 6.92[b] 6.98—7.10
3d	9.11	6.58	7.18	8.24	7.77	1.02 4.00—4.24	7.13—7.28	2.41
3e	9.11	6.60	7.20	8.23	7.79	1.05 4.00—4.24	7.10 7.22	2.42
3f	9.11	6.60	7.20	8.23	7.78	1.05 4.02—4.24	7.04 7.37	2.42
3g	9.20	6.57	7.18	8.24	7.76	1.02 4.00—4.23	7.13—7.27	1.22 2.76
3h	9.19	6.58	7.19	8.22	7.78	1.05 4.01—4.24	7.10 7.22	1.22 2.77
3i	9.19	6.58	7.19	8.22	7.77	1.05 4.01—4.24	7.04 7.37	1.22 2.77
3j	8.64	6.21	2.31	7.99	7.63	1.02 4.02—4.17	6.98—7.16	3.86 6.94[b] 6.98—7.16
3k	8.65	6.23	2.31	7.97	7.63	1.05 4.01—4.21	d) 7.22	3.87 6.93[b] 6.98—7.12
3l	8.65	6.23	2.31	7.97	7.62	1.05 4.01—4.10	7.07 7.37	3.87 6.93[b] 6.98—7.12
3m	9.00	6.43	2.35	8.06	7.66	0.99 4.00—4.23	7.13—7.27	2.39
3n	9.00	6.45	2.36	8.04	7.67	1.02 4.03 4.19	7.09 7.21	2.40
3o	9.00	6.45	2.36	8.04	7.66	1.02 4.02 4.19	7.04 7.36	2.40
3p	9.09	6.42	2.35	8.06	7.64	0.98 4.01 4.17	7.12—7.28	1.21 2.74
3q	9.08	6.43	2.36	8.04	7.66	1.01 4.02 4.19	7.09 7.21	1.21 2.75
3r	9.08	6.43	2.36	8.04	7.65	1.01 4.02 4.19	7.04 7.36	1.21 2.75

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}$=6.8—7.1 Hz, $J_{7,8}$=9.3—9.5 Hz, $J_{5,7}$=0.8—1.0 Hz, $J_{6,8}$=1.1—1.3 Hz, J_{Et}=6.8—7.2 Hz, J_{Ar}(vicinal)=7.3—8.4 Hz. b) 4H. c) Overlapped with the phenyl proton signals at δ 6.98—7.10. d) Overlapped with the phenyl proton signals at δ 6.98—7.12.

α,β-unsaturated ester carbonyl band (1663—1674 cm^{-1}). In the ^{1}H-NMR spectra (Table 2) of **3a—r** each proton signal due to the two thieno[3,4-*b*]-indolizine moieties completely overlapped to suggest a structure with the same substituted pattern and position. That the chemical shifts and patterns of the thieno[3,4-*b*]indolizine moieties in **2a—r** and **3a—r** are very similar to each other also supported these structures.

Reaction mechanisms. Possible reaction routes for these reactions are shown in Scheme 3. The protonation of alcohols **2a—r**, which were formed by the selective reduction of ethyl 1-arylcarbonylthieno[3,4-b]indolizine-9-carboxylates (**1a—r**) with sodium borohydride, followed by the dehydration of the resulting ion such as **4** could provide an electrophilic carbonium ion **5**. The aromatic electrophilic substitution (SE_{Ar} reaction) between ion **5** and the more favorable resonance structure (**2'**) of alcohols **2a—r** can give the primary adduct **6**, and the aromatization (or retro SE_{Ar} reaction) of **6** with the elimination of a protonated benzaldehyde should form the observed products **3a—r**. Though the reason why this type of condensation occurred is unclear, we can point out the high nucleophilicity of the thiophene ring in alcohols **2a—r**, because our attempts to trap the key ionic intermediate **5** with other electron-rich aromatic compounds such as phenol, furan and pyrrole were unsuccessful.



Scheme 3

EXPERIMENTAL

Melting points were measured on a Yamagimoto micro melting point apparatus and were not corrected. IR spectra were measured on a JASCO FT/IR-5300 IR spectrophotometer from samples as KBr pellets. ^{1}H-NMR spectra were measured on a JEOL JNM-GX400 (400 MHz for ^{1}H) in deuteriochloroform solutions. Tetramethylsilane was used as the internal standard and *J* values were given in Hz. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer.

Preparation of ethyl 3-alkylthio-1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine-9-carboxylate (2a—r). *Typical procedure*: To an ethanolic solution (20 ml) of ethyl 3-alkylthio-1-(arylcarbonyl)thieno[3,4-*b*]indolizine-9-carboxylate **1** (1.0 mmol), 11.4 mg (0.3 mmol) of sodium borohydride was added at 80 °C in a water bath. After the completion of the reduction reaction was confirmed by thin layer chromatograghic monitoring, the resulting mixture was concentrated at reduced pressure. The residue was poured into water (30 ml) and the precipitates which separated were collected by suction. Recrystallization from ethanol-hexane afforded the corresponding alcohols **2a—r**.

^{1}H-NMR spectral data for compounds **2a—r** were shown in Table 1 and some other data are as follows.

2a: 99%; yellow prisms; mp 116–117 °C; IR (KBr): 3385, 1643 cm^{-1}. *Anal.* Calcd for $C_{27}H_{23}NO_3S_2$: C, 68.47; H, 4.90; N, 2.96%; found C, 68.55; H, 4.94; N, 2.96%.

2b: 97%; yellow prisms; mp 45–47 °C; IR (KBr): 3393, 1647 cm^{-1}. *Anal.* Calcd for $C_{27}H_{22}ClNO_3S_2$: C, 63.83; H, 4.36; N, 2.76%; found C, 63.97; H, 4.37; N, 2.60%.

2c: 72%; yellow prisms; mp 53–55 °C; IR (KBr): 3317, 1638 cm^{-1}. *Anal.* Calcd for $C_{27}H_{22}BrNO_3S_2$: C, 58.70; H, 4.01; N, 2.54%; found C, 58.88; H, 4.00; N, 2.38%.

2d: 97%; yellow prisms; mp 127–129 °C; IR (KBr): 3451, 1669 cm^{-1}. *Anal.* Calcd for $C_{21}H_{19}NO_3S_2$: C, 63.45; H, 4.82; N, 3.52%; found C, 63.43; H, 4.94; N, 3.42%.

2e: 83%; yellow prisms; mp 167–169 °C; IR (KBr): 3364, 1642 cm^{-1}. *Anal.* Calcd for $C_{21}H_{18}ClNO_3S_2$: C, 58.39; H, 4.20; N, 3.24%; found C, 58.37; H, 4.24; N, 3.22%.

2f: 99%; yellow prisms; mp 142–144 °C; IR (KBr): 3339, 1649 cm^{-1}. *Anal.* Calcd for $C_{21}H_{18}BrNO_3S_2$: C, 52.94; H, 3.81; N, 2.94%; found C, 52.91; H, 3.86; N, 2.92%.

2g: 98%; yellow prisms; mp 109–111 °C; IR (KBr): 3345, 1638 cm^{-1}. *Anal.* Calcd for $C_{22}H_{21}NO_3S_2$: C, 64.21; H, 5.14; N, 3.40%; found C, 64.19; H, 5.15; N,3.41%.

2h: 92%; yellow prisms; mp 95–97 °C; IR (KBr): 3291, 1644 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}ClNO_3S_2$: C, 59.25; H, 4.52; N, 3.14%; found C, 59.23; H, 4.45; N, 3.23%.

2i: 83%; yellow prisms; mp 100–101 °C; IR (KBr): 3355, 1647 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}BrNO_3S_2$: C, 53.88; H, 4.11; N, 2.86%; found C, 53.84; H, 4.04; N, 2.96%.

2j: 85%; yellow prisms; mp 139–141 °C; IR (KBr): 3418, 1620 cm^{-1}. *Anal.* Calcd for $C_{28}H_{25}NO_3S_2$: C, 68.97; H, 5.17; N, 2.87%; found C, 69.00; H, 5.15; N, 2.86%.

2k: 99%; yellow needles; mp 126–128 °C; IR (KBr): 3281, 1630 cm^{-1}. *Anal.* Calcd for $C_{28}H_{24}ClNO_3S_2$: C, 64.42; H, 4.63; N, 2.68%; found C, 64.51; H, 4.61; N, 2.61%.

2l: 86%; yellow prisms; mp 131–133 °C; IR (KBr): 3290, 1628 cm^{-1}. *Anal.* Calcd for $C_{28}H_{24}BrNO_3S_2$: C, 59.36; H, 4.27; N, 2.47%; found C, 59.08; H, 4.55; N, 2.46%.

2m: 93%; yellow prisms; mp 165–166 °C; IR (KBr): 3360, 1626 cm^{-1}. *Anal.* Calcd for $C_{22}H_{21}NO_3S_2$: C, 64.21; H, 5.14; N, 3.40%; found C, 64.20; H, 5.16; N, 3.39%.

2n: 93%; yellow prisms; mp 163–165 °C; IR (KBr): 3398, 1633 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}ClNO_3S_2$: C, 59.25; H, 4.52; N, 3.14%; found C, 59.39; H, 4.52; N, 3.00%.

2o: 99%; yellow prisms; mp 173–174 °C; IR (KBr): 3414, 1635 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}BrNO_3S_2$: C, 53.88; H, 4.11; N, 2.86%; found C, 53.96; H, 4.14; N, 2.75%.

2p: 71%; yellow prisms; mp 126–128 °C; IR (KBr): 3414, 1634 cm^{-1}. *Anal.* Calcd for $C_{23}H_{23}NO_3S_2$: C, 64.91; H, 5.45; N, 3.29%; found C, 65.13; H, 5.37; N, 3.15%.

2q: 86%; yellow prisms; mp 165–167 °C; IR (KBr): 3409, 1632 cm^{-1}. *Anal.* Calcd for $C_{23}H_{22}ClNO_3S_2$: C, 60.05; H, 4.82; N, 3.04%; found C, 60.05; H, 4.85; N, 3.01%.

2r: 93%; yellow prisms; mp 165–167 °C; IR (KBr): 3409, 1632 cm^{-1}. *Anal.* Calcd for $C_{23}H_{22}BrNO_3S_2$: C, 54.76; H, 4.40; N, 2.78%; found C, 54.71; H, 4.51; N, 2.78%.

Preparation of bis[3-alkylthio-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-1-yl]toluene derivatives (3a—s). *Typical procedures*: A solution of 1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine **2** (0.25 mmol) and acetic acid (60 mg, 1.0 mmol) in $CHCl_3$ (10 ml) was stirred at room temperature for 24 h. After the evaporation of the solvent the residual oil was separated by column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ fractions involving **3** were collected and the solvent was removed at reduced pressure. Recrystallization from ether gave the corresponding condensation product **3**.

The NMR monitoring of these reactions disclosed the presence of a singlet signal for an aromatic aldehyde proton near δ 10, though we could not isolate them because of their very amall amounts. ^{1}H-NMR spectral data for compounds **3a**—**r** were shown in Table 2 and some other data are described below.

3a: 40%; black prisms; mp 114–116 °C; IR (KBr): 1663 cm^{-1}. *Anal.* Calcd for $C_{47}H_{38}N_2O_4S_4$: C, 68.59; H, 4.65; N, 3.40%; found C, 68.55; H, 4.81; N, 3.15%.

3b: 31%; black prisms; mp 177–179 °C; IR (KBr): 1667 cm^{-1}. *Anal.* Calcd for $C_{47}H_{37}ClN_2O_4S_4$: C, 65.83; H, 4.35; N, 3.27%; found C, 65.89; H, 4.51; N, 3.05%.

3c: 22%; black prisms; mp 163–166 °C; IR (KBr): 1665 cm^{-1}. *Anal.* Calcd for $C_{47}H_{37}BrN_2O_4S_4$: C, 62.59; H, 4.13; N, 3.11%; found C, 62.64; H, 4.36; N, 2.82%.

3d: 51%; yellow prisms; mp 235–237 °C; IR (KBr): 1669 cm^{-1}. *Anal.* Calcd for $C_{35}H_{30}N_2O_4S_4$: C, 62.66; H, 4.51; N, 3.52%; found C, 62.70; H, 4.54; N, 3.42%.

3e: 81%; yellow prisms; mp 228–229 °C; IR (KBr): 1669 cm^{-1}. *Anal.* Calcd for $C_{35}H_{29}ClN_2O_4S_4$: C, 59.60; H, 4.14; N, 3.97%; found C, 59.70; H, 4.27; N, 3.75%.

3f: 31%; yellow prisms; mp 225–226 °C; IR (KBr): 1669 cm^{-1}. *Anal.* Calcd for $C_{35}H_{29}BrN_2O_4S_4$: C, 56.07; H, 3.90; N, 3.74%; found C, 56.16; H, 4.01; N, 3.54%.

3g: 41%; yellow prisms; mp 143–145 °C; IR (KBr): 1670 cm^{-1}. *Anal.* Calcd for $C_{37}H_{34}N_2O_4S_4$: C, 63.58; H, 4.90; N, 4.01%; found C, 63.54; H, 5.05; N,3.91%.

3h: 51%; yellow prisms; mp199–201 °C; IR (KBr): 1672 cm^{-1}. *Anal.* Calcd for $C_{37}H_{33}ClN_2O_4S_4$: C, 60.60; H, 4.54; N, 3.82%; found C, 60.71; H, 4.67; N, 3.59%.

3i: 27%; yellow prisms; mp 201–203 °C; IR (KBr): 1674 cm^{-1}. *Anal.* Calcd for $C_{37}H_{33}BrN_2O_4S_4$: C, 57.13; H, 4.28; N, 3.60%; found C, 57.40; H, 4.30; N, 3.31%.

3j: 25%; black prisms; mp 189–191 °C; IR (KBr): 1671 cm^{-1}. *Anal.* Calcd for $C_{49}H_{42}N_2O_4S_4$: C, 69.15; H, 4.97; N, 3.29%; found C, 69.16; H, 5.10; N, 3.15%.

3k: 18%; black prisms; mp 177–179 °C; IR (KBr): 1665 cm^{-1}. *Anal.* Calcd for $C_{49}H_{41}ClN_2O_4S_4$: C, 66.46; H, 4.67; N, 3.16%; found C, 66.41; H, 4.77; N, 3.10%.

3l: 13%; black prisms; mp 200–202 °C; IR (KBr): 1663 cm^{-1}. *Anal.* Calcd for $C_{49}H_{41}BrN_2O_4S_4$: C, 63.28; H, 4.44; N, 3.01%; found C, 63.23; H, 4.71; N, 2.79%.

3m: 54%; yellow prisms; mp 159–161 °C; IR (KBr): 1661 cm^{-1}. *Anal.* Calcd for $C_{37}H_{34}N_2O_4S_4+2H_2O$: C, 60.47; H, 5.21; N, 3.81%; found C, 60.52; H, 5.26; N, 3.71%.

3n: 89%; yellow prisms; mp 155–157 °C; IR (KBr): 1674 cm^{-1}. *Anal.* Calcd for $C_{37}H_{33}ClN_2O_4S_4$: C, 60.60; H, 4.54; N, 3.82%; found C, 60.69; H, 4.76; N, 3.50%.

3o: 39%; yellow prisms; mp 156–158 °C; IR (KBr): 1674 cm^{-1}. *Anal.* Calcd for $C_{37}H_{33}BrN_2O_4S_4$: C, 57.13; H, 4.28; N, 3.60%; found C, 57.45; H, 4.28; N, 3.28%.

3p: 38%; yellow prisms; mp 135–137 °C; IR (KBr): 1672 cm^{-1}. *Anal.* Calcd for $C_{39}H_{38}N_2O_4S_4$: C, 64.43; H, 5.27; N, 3.85%; found C, 64.49; H, 5.31; N, 3.75%.

3q: 65%; yellow prisms; mp 148–150 °C; IR (KBr): 1669 cm^{-1}. *Anal.* Calcd for $C_{39}H_{37}ClN_2O_4S_4+H_2O$: C, 60.10; H, 5.04; N, 3.59%; found C, 60.08; H, 5.31; N, 3.34%.

3r: 76%; yellow prisms; mp 149–151 °C; IR (KBr): 1672 cm^{-1}. *Anal.* Calcd for $C_{39}H_{37}BrN_2O_4S_4$: C, 58.13; H, 4.63; N, 3.48%; found C, 58.27; H, 4.76; N, 3.21%.

Crystallography of ethyl 3-benzylthio-1-(α-hydroxybenzyl)-7-methylthieno[3,4-*b*]indolizin-9-carboxylate (2j) A single crystal (0.08×0.32×0.42 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK_α radiation (λ=0.71069 Å). Crystal data of **2j**: $C_{28}H_{25}NO_3S_2$; M=487.63; monoclinic, space group *C2/c* (#15), Z=8 with a=22.77 (1) Å, b=9.89 (1) Å, c=21.91 (1) Å, β=102.66° (4); V=4813 (6) $Å^3$, and $D_{calc.}$=1.35 g/cm^3. All calculations were performed using CrystalStructure.[10] The structure was solved by a direct method (SIR).[11] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.075 and 0.067 for 2118 (I>2.00σ(I)) observed reflections, respectively.

REFERENCES AND NOTES

1. For part 68 of this series, see Kakehi, A., Suga, H., Okumura, Y., Nishi, T., *Heterocycles*, **81**, 175—184 (2010).
2. Kakehi, A., Ito, S., Suga, H., Miwa, T., Mori, T., Fujii, T., Tanaka, N., Kobayashi, T., *Chem. Pharm. Bull.*, **51**, 75—84 (2003).
3. Kakehi, A., Suga, H., Kako, T., Fujii, T., Tanaka, N., Kobayashi, T., *Chem. Pharm. Bull.*, **51**, 1246—1252 (2003).
4. Kakehi, A., Ito, S., Suga, H., Miwa, T., Mori, T., Fujii, T., Tanaka, N., Kobayashi, T., *Chem. Pharm. Bull.*, **51**, 75—84 (2003).
5. Kakehi, A., Suga, H., Kaneko, Y., Fujii, T., Tanaka, N., *Chem. Pharm. Bull.*, **53**, 1430—1238 (2005).
6. Kakehi, A., Suga, H., Isogai, H., *Chem. Pharm. Bull.*, **55**, 95—101 (2007).
7. Kakehi, A., Suga, H., Okumura, Y., Shinohara, M., Kako, T., Sekiguchi, T., Shiro, M., *Chem. Pharm. Bull.*, **57**, 1385—1390 (2009).
8. Kakehi, A., Suga, H., Hatayama, S., Kobo, D., *Heterocycles*, **65**, 1557—1560 (2005).

9. Johnson, C. K., "ORTEO II, Report ORNL-5138," Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
10. "CrystalStructure 3.8", Crystal Structure Analysis Package, Regaku and Regaku/Molecular Structure Corporation (2000-2005). 9009 New Trails Dr. The Woodlands TX 77381 USA.
11. "SIR92", Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M., Polidori, G., and Camalli, M. *J. Appl. Cryst.*, **26**, 343—350 (1993).

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